NYMPHA-MD

Next Generation Mobile Platforms for HeAlth, in Mental Disorders

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NYMPHA-MD

Technical Specification

www.nympha-md-project.eu	
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Contents

1 Objectives of NYMPHA-MD

1.1 Background on Bipolar Disorder and ICT-empowered treatment:

Bipolar Disorder is a common and complex form of mental disorder. Epidemiological studies suggest that bipolar disorder has a prevalence of about 1% in European countries. People with bipolar disorder experience episodes of pathological mood changes that fall into two broad categories: symptoms of mania (euphoria) and symptoms of depression. Although bipolar disorder is equally prevalent in both men and women the course of illness differs greatly between the two genders. However, in both genders the disorder has a typically relapsing-remitting course. Bipolar disorder is often a long-term and persistent illness and the management and treatment can continue for many years.

During the last decade within the area of bipolar disorder research and treatment there has been an emerging shift in illness paradigm from a focus on affective episodes to an increasing focus on inter-episodic mood instability. Many patients with bipolar disorder experience significant subsyndromal day-to-day or week-to-week mood swings that are of greater severity than those experienced by healthy individuals, and also appear to reflect the level of illness activity. Continuous monitoring and assessment of mood instability and other variables possibly reflecting illness activity may therefore be clinically relevant since it would allow for early intervention on subsyndromal symptoms and ultimately prevention of full-blown affective episodes. Self-reports are ubiquitous in psychiatric research, and various mood charting instruments for self-monitoring are frequently used in the management and monitoring of depressive and manic symptoms in patients with bipolar disorder. Traditionally these mood charting instruments have been paper-based, such as the National Institute of Mental Health LifeChart Method (NIMH-LCM), the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BP), the Mood Chart and the ChronoSheet. Paper-based mood charting instruments can be viewed as facilitating tools helping patients with bipolar disorder gain illness insight, facilitate patient empowerment, teach patients to recognize early warning signs of recurrence of affective episodes and enable individualized characterization of mood instability in detail. However, several issues related to and limiting the usefulness of paper-based mood charting instruments have been addressed, such as low compliance and potential recall bias when reporting data retrospectively, i.e. where patients complete batches of daily ratings at a single time (sometimes referred to as hoarding or backfilling). Recent years have seen an increasing growth of e-mental health technologies, and the amount of electronic platforms (e.g. PDAs, computers, regular cell phones, and smartphones) offering tools for self-monitoring is increasing rapidly. The electronic approach for self-monitoring offers ecological momentary assessments, a monitoring technique for the assessment of variables in real-time and in naturalistic settings, offers the ability to verify the timing and compliance of data collection, eliminate the need for costly and error-prone data entry, may help remind patients to perform the self-monitoring and have a higher usability than different paper-based versions.

Overall in scientific studies using different mobile tools for self-monitoring it was found that electronic self-monitoring resulted in higher compliance to perform the self-monitoring, there

was more complete data and a higher acceptance of the monitoring tool than when monitoring using traditional methods. Also different scientific studies have found a correlation between the electronic self-monitoring and observer-based clinically rated symptoms of bipolar disorder. Overall, in light of the high prevalence and unmet need in the treatment of bipolar disorder, there has been recent interest in the utility of mobile tools in the treatment of this costly disorder.

Integrating the abilities of a phone, computer, journal, internet connection, survey platform, and a host of sophisticated sensors, smartphones have features that can be applied towards mental health. Nowadays there is a growing interest for e-health mobile applications available on the mobile market that claims to support aspects related to people's health state. However the use of such applications is currently lacking of a clear regulatory framework and clinical evidence for efficacy benefits. This immaturity constitutes a major barrier to fully exploit the benefits of mobile technologies in the medical domain. Nevertheless, this does not mean that there could not be feasible and useful mobile apps suitable to be developed and used as a part of care paths in some disease. In fact, this issue has been identified by the EC and by several procurers around Europe amongst which the ones involved in this PCP who are aware (and interested in) of the potentiality to introduce innovative applications based on smart phones and in portable/wearable devices to support specific diseases where mobile technology can play a relevant role.

The NYMPHA-MD project focuses on the implementation of a Pre-Commercial Procurement of mobile e-health services for supporting physicians and patients in the treatment of bipolar disorder. NYMPHA-MD solutions will be based on continuous patients monitoring in order to dynamically support illness management and potentially identify early warning signs of deviations in mood and attitudes suggesting the onset of a depressive or manic episode. Such an innovative approach in the treatment of bipolar disorder will allow for early intervention of professionals and a personalized and continuous feedback to patients about early warning signs and indications for referral to professionals, caregivers and self-management. From this point of view, access to interactive tools that are able to deliver psycho-education and self-help sessions according to standardized and effective models should also be available. The monitoring model of such type of approach would be based on a portable data acquisition system able to obtain real-time subjective and continuous automatically generated objective measurements of patients behavior related to their clinical mental state collected in naturalistic settings, also giving feedbacks and visualization of data to patients, informal caregivers and clinical professionals, thus enhancing awareness and empowering attitude and supporting their care with the support of ICT.

1.2 State of the Art on Bipolar Disorder Treatment and NYMPHA-MD opportunities ahead:

Baseline of clinical practice and current limitations in treatment

In current medical practice, the standard assessments of depression and mania severity are clinical rating scales developed in the early 1960s (e.g. the Hamilton Depression Rating Scale Depression (HAMD); the Young Mania Rating Scale) and other more recent variations (e.g. the Bipolar Spectrum Diagnostic Scale, BSDS). These rating scales are based on interview with the patient and the clinicians' clinical observations. While the validity of these scales in supporting clinical diagnosis and in guiding treatment of bipolar disorder has been proven, they may miss information relative to changes in daily activities, behavior and mood, thus hampering full estimation of severity of illness evaluation. Moreover, current practice of bipolar disorder

treatment is based on identification and analysis of mood instability episodes at different intervals of time without possibility of continuous monitoring in a practical and continuous way. On this regard, with the use of currently available technology proposed by recent research approaches and an adequate definition and implementation of innovative services and processes it is envisioned in the short term a new generation of services to improve healthcare provisioning in the treatment of mental health diseases. In this way the new therapeutic approaches will be able to integrate continuous monitoring of health condition through the use of assessment criteria based on quantitative indicators of patient activity provided with objective real-time monitoring from naturalistic settings without the unbiased interpretation due to patient condition, thus extending the scope of the current practice in clinical and community settings.

Current treatment options in bipolar disorder, including pharmacological and psychological interventions, are not fully effective in halting a negative course of the illness. Among the avoidable reasons for the decreased effect of interventions in clinical practice we must highlight the delay in the intervention for the prodromal phases of both depressive and manic episodes. Other critical issues are the lack of information delivered to patients and families as well as poor adherence to pharmacological and psychological treatment. Several scientific studies suggest that illness insight in bipolar disorder is state-dependent rather than trait-dependent that illness insight is more impaired during mania than depression, and that impaired illness insight is associated with lower adherence to psycho-pharmacological treatment. Tools aiming at educating the patients in their illness aim at increasing illness insight, illness awareness, understanding of their disorder and to teach patients methods to identify early warinng signs and thereby increasing adherence and preventing affective episodes. Electronic monitoring tools share some of these properties and therefore may help patients to correct hypomanic/manic and depressive thoughts and behavior and in this way increase insight and adherence.

Treatment discontinuation is associated with a highly increased risk of relapse of severe mood episodes and hospitalization. In this context, poor treatment adherence could be due to lack of insight or motivation but it may be avoided by adequate prevention and information.

During the last decades there has been a major organizational switch in paradigm all over Europe and the rest of the world from inpatient treatment to outpatient treatment in health care. Within mental health the number of beds in hospitals has been reduced to a third of the number during the 80' ties and this change is still ongoing. This requires a prioritized distribution of resources in outpatients' treatment settings. Currently, there is scientific switch in paradigm of treatment in bipolar disorder from focus on the mood episodes to focus on the inter-episodic mood instability. Patients with bipolar disorder experiences higher level of mood instability than healthy individuals, and high level mood instability between affective episodes has been shown to be associated with higher risk of recurrence of depressive and manic episodes and a higher risk of hospitalization. Regarding early intents on using ICTs for better management of bipolar disorders even if preliminary research on this field is promising, there are clear indicators of what has not worked so far in previous developments. Examples of these include the use of technology in a way that may stigmatize patients and increase usability problems (e.g. by using obtrusive sensors), problems related to low adherence due to the need of wearing simultaneously a large number of sensing devices (hearth monitors, galvanic skin response meters, wrist worn devices, cameras, etc.), users perception of low privacy, no adequate feedback loop to patients, poor involvement of patients in design phase, use of ICTs with high demanding setup, configuration and maintenance requirements from patients and clinicians (installation of drivers, continuous charging of many batteries, etc.), low (or null)

integration of solutions in clinical workflow, uncertainty and lack of knowledge about regulatory aspects and limited attention to other non-functional requirements such as interoperability between sensing platforms, compatibility with electronic health records and consideration of data management constraints and policies.

Related ICT interventions and their limitations

Recent research work conducted at European level has addressed the problem of supporting treatment of bipolar disorder utilizing ICT technologies. Some of the most relevant examples of there are PSYCHE [www.psyche-project.org] and MONARCA [www.monarca-project.eu] projects.

PSYCHE Project: This project was based on textile platforms and portable sensing devices for the long term and short-term acquisition of physiological data from selected class of patients affected by mood disorders. PSYCHE physiological data extraction was based mostly on a hardware platform that uses a number of sensors that the patient has to wear in order to achieve data collection. While the potential of using physiological data to correlate with mental health condition remains an interesting problem, PSYCHE encounter several limitations due to the current level of the technologies in creating non-intrusive sensing mechanisms that affected substantially the level of usability of the proposed solutions and as a consequence the low acceptance of technology.

MONARCA Project: MONARCA was based on a multi-parametric mobile eHealth platform for continuous acquisition of objective behavioral data reflecting the main indicators of established scales (such as BRAHMS, HAMD) utilized for treatment of bipolar disorder. An important characteristic in MONARCA was its non-intrusiveness to the patient due on the fact that all sensing is done utilizing a standard smartphone in a regular way becoming a fully mobile eHealth platform without need of attaching sensors directly to the patient. While in MONARCA usability and users acceptance of technology was high, a limitation was the actual opportunity to conduct more elaborated real-time interventions favoring patients awareness such as psycho-education and more detailed decision support advice to both, patients and clinicians. In MONARCA the role of informal caregiver hasn't been explored and this leaves open the field to investigate further how to use mobile sensing for involving other relevant stakeholders in treatment management.

Other related research projects have focused on the use of portable devices for treating aspects of mental health. In such projects the predominant approach is based on the use of physiological and behavioral analysis for estimating the patient condition mostly by means of wearable sensors and patients diaries (ICT4Depression) and occasionally with use of implants (as proposed in OPTIMI) and for education of patients on disease management (Interstress). In such approaches the mobile phone was used mostly as a gateway integrating input from other wearable sensors or as the patient user interface. The main limitations of such projects were the difficulty integrating their solutions into existing clinical paths and the lack of use of standards and applicable regulatory frameworks with the consequence of a solution not fitting the actual treatment processes and unable to communicate with the current clinical systems.

1.3 Opportunities Ahead on Bipolar Disorder Management

1.3.1 Opportunities enabled by ICTs

Electronic tools facilitating monitoring of mood instability could allow for early intervention on prodromal symptoms and potentially influence the course of illness. Moreover electronic tools for monitoring illness activity could allocate the resources in outpatient settings in a more efficient way to where they are needed and may facilitate the possibility for patients' visits to be scheduled more flexible and when indicated. Electronic tools for this kind of monitoring will allow for real-time monitoring in naturalistic settings without the risk of recall bias as has been shown to be present when using different paper-based versions for self-monitoring. During the years different electronic self-monitoring platforms for regular cell phones, PDAs, computers and smartphones have been developed. These systems allow for continuous self-monitoring of symptoms of bipolar disorder, but except for smartphones, they do not have the capacity to collect objective data on patient behavior and most of the systems have not included a feedback loop between the patients and the mental healthcare providers. These two aspects, the feedback loop and the automatically generated objective data, of a monitoring system represent highly innovative and novel approaches to the treatment and management of bipolar disorder. There is good possibility that automatically generated objective data, collected using different modalities and sensors in smartphones and/or other sensing platforms, could potentially serve as an electronic biomarker of illness activity. Furthermore patients could experience an increased illness insight and empowerment. The construction of such systems in the upcoming years is expected to allow for more preventive approach regarding episodes treatment through analysis of patients' behavior trends and timely prediction of personalized risk factors to clinicians.

1.3.2 Opportunity of Improvement on state-of-the-art treatment

Subjective recording of mood, sleep, activity level and alcohol consumption correlate with illness activity in bipolar disorder. However, the ability of these subjective measures to detect prodromal symptoms of depression and mania may be not be sufficient compared to more objective measures such as speech, social and physical activity that is likely to be achievable with the use of ICTs. For example, decreased activity in speech (paucity of speech) is a sensitive and valid measure of prodromal symptoms of depression, and conversely increased speech activity (talkativeness) predict switch to hypomania. Similarly, social activities, i.e., engaging in relations to others, as well as physical activity represent central and sensitive aspects of illness activity in bipolar disorder. Automatically generated objective data collected using ICTs (in particular smartphones) has good opportunity to correlate with symptoms of depression and mania in patients with bipolar disorder.

Additionally, the NYMPHA system could facilitate and enable agreement (concordance) between patient, relatives/informal caregivers and clinicians, which is highly important for a better treatment outcome. It is very often a crucial problem that patients, relatives/informal caregivers and clinicians comprehend the patient's condition in different ways and consequently they will each aim for different (treatment) methods and goals. Using the NYMPHA system all three involved partners could be able to continuously and visually follow the illness activity and the effect of treatment resulting in a high adaptation of the treatment to the illness phase. A NYMPHA system could optimize outpatient treatment and increase patient participation and empowerment. Patients frequently gain contact with a number of different

treatment facilities such as various inpatient hospitals, outpatient hospital clinics, community mental health centres and specialized treatment clinics: such a fragmentation may well represent a barrier to adequate information to patients. In such huge systems, patients often get a feeling that the treatment system is more important than themselves as an individual patient. Using the NYMPHA system, the patient should be the central player carrying all individual illness and treatment information across treatment barriers, and the NYMPHA system could be a continuous ongoing monitoring system, which the patient will bring with him/her as a continuous and familiar monitoring tool through the course of treatment over the years.

Customization of the designed e-health functions in the proposed NYMPHA system will be highly necessary in view of the differences in approaches to illness care and management in the three service networks and given the high individual variability in needs, treatment goals and resources of the treated subjects and in the same subject in different periods and phases.

As mentioned before the following functionalities could be relevant to develop in the NYMPHA solutions:

- self-monitoring of subjective data,
- automatically generated objective data monitoring,
- communication with formal and informal caregivers and support groups, patients and clinicians,
- tracking of mood state,
- capacity to detect and predict episodes in the early phase with prodromal depressive and manic symptoms.

The self-monitoring part of the application should be designed in a way so that it is flexible and adjustable for each patient. The number of self-monitoring items should be optional and adjustable over time. However, four self-monitoring items should be mandatory for all patients: mood, sleep duration, activity and medicine.

The following automatically generated objective data are examples of what could be collected by the NYMPHA solutions (but not limited only to these):

a) Social activities: defined as the numbers of daily outgoing and incoming calls, text messages, missed/not answered calls, number of different outgoing and incoming telephone numbers, etc.
b) Physical activity: measured by accelerometers.
c) Mobility: measured as the amount of movement between cell tower ID's per day or gps locations.
d) Phone usage: measured as how much the patients phone is used; such as the number of applications being installed on the smartphone, the number of minutes the screen is on per day, the amount of time on and amount of data used on social medias such as Facebook, Twitter, Instagram, browsing etc.
e) Speech patterns: Voice feature extraction.

Other kinds of automatically generated objective data may off course be suggested.

Disease information. feedback and prediction analysis:

A number of historical graphs may present the collected self-monitoring data and automatically generated data visually. The collected data from the last days/weeks should be visualized graphically. The feedback loop:

a. A web-interface for clinicians should be available. Clinicians in this context are considered as different caregivers at hospitals, private psychiatrists, nurses etc. This should present the collected data on all users (the patients) in a clear and accessible way allowing for the clinicians to monitor and identify early signs of emerging depressive or manic episodes. In this way the feedback loop should facilitate intervention shortly after prodromal depressive or manic symptoms appear. A "bipolar disorder chart" with an overview of the patient's clinical history such as previous episodes and hospitalizations, treatment history, blood samples etc. should be available for the clinicians.
b. The system should allow for automatic feedback on the collected data to the patient and to perform prediction analyses to the clinicians based on data collected by the NYMPHA solution.

All collected data should be sent to a secure server and the web-interface should require a secure log in.

A collection of relevant references to previous work can be found in Nympha-Md website at: http://www.nympha-md-project.eu/scientific-background

1.4 NYMPHA-MD Challenge: IT-supported treatment process for predicting bipolar disorder evolution

NYMPHA-MD objective is to enable the creation of the next generation of mHealth solutions in the field of mental health with a focus on management and treatment of bipolar disorder.

The envisioned solutions are expected to combine 1) monitoring of self-reported and multi-parametric, automatically generated data characterizing human behaviors pertaining to bipolar disorder and 2) advanced algorithms based on data analysis techniques to conduct assessment and prediction analysis of affective states. The innovative solutions provided by NYMPHA-MD should take into consideration a plan for integration with existing clinical processes and workflows in the target regions and with the relevant National and European directives and standards in terms of data protection and patients' safety.

The expected solutions should alleviate in at least 10% the number of patients re-admissions due to relapse and the time spent by clinicians in following patients and should provide a clear strategy on how they plan to reach this target.

A combination and presentation of both subjective self-monitored data and automatically generated objective data to the patients, the clinicians and informal caregivers could be a major improvement in the evaluation of affective states of patients with bipolar disorder. Also a system capable of analyzing and providing the clinicians with prediction analysis on the collected data would be a major step and innovation for the management of bipolar disorder. A system capable of this does not exist and is one of the main expected outcomes of NYMPHA-MD.

Other expected outcomes of the ideal system could include the reduction of the risk of relapse, the increase of adherence to treatment, the high acceptance of the proposed system by patients

and clinicians and the proof of clinical validity of the solution. Using a monitoring system like the one envisioned by NYMPHA-MD would most likely be able to make outpatient treatment more flexible and efficient and allowing patients to show up for treatment when needed and indicated. Also resources could be allocated to the right places at the right time due to a well-established and innovative organization of the clinical work processes impacting in costs reduction for healthcare organizations for at least 15% on specific costs related to treatment and detailed below.

A number of research challenges involved in the construction of the NYMPHA-MD solutions are foreseen to require multi-disciplinary work aiming (but not limited) to:

- Identification of behavioral markers of bipolar disorder from remote continuous monitoring tools
- ICTs –based intervention planning for behavior change
- Early detection of patients risk conditions
- Prediction of mood change based on continuous monitored behavioral information
- Maximization of treatment adherence using ICTs
- Clinical relevance of using ICTs for treatment improvement
- Personalization of treatment based on patients models

2 Use Cases

Some possible (non-exhaustive) scenarios of NYMPHA usage are described below:

Use Case 1: Mario is a patient with bipolar disorder who monitors and tracks his mood on a daily basis using the NYMPHA app. Mario is supposed to visit the hospital in 15 days from now. In the meantime, during the past 3 days the NYMPHA system has recorded several automatically generated objective data representing possible symptoms of depression, such as reduction of physical activity detected using the phone accelerometer, low-level of social activity in the amount of outgoing calls and messages, and the fact that Mario has been at home all most all day long through the positioning data given by the GPS in the phone. In addition, during the same days, Mario reported through the self-assessment window in the NYMPHA app that he has being feeling depressed. Furthermore, the NYMPHA system has analyzed data collected from Mario over the period of time he has been using the system and presents to Mario, based on predictions models, that data suggests that he could experience some symptoms the next days and perhaps should contact the nurse or clinician

This morning Maria, who is the nurse looking at the graphs of the patients using the NYMPHA system on a daily basis, verifies the aggregated state of Mario's mood in the past three days as shown by the NYMPHA web interface and she notes too that both, the NYMPHA system and Mario's self-assessments indicate a constant state of presence of depressive symptoms. Also the nurse is presented with prediction analysis suggesting that in the following days Mario will most likely experience symptoms of depression. Based on this information, Maria decides to call Mario to talk about his symptoms and decides anticipating his appointment in the hospital for tomorrow.

Use Case 2: Eva is a patient with bipolar disorder who is gradually entering into a (hypo-)manic episode. During the past 8 days the NYMPHA system has detected that she has increased the

number of calls and messages to her friends, sometimes even calling at very unusual time late at night. In addition Eva has been not participating in discussions of her NYMPHA online support-group which she usually does…

Besides the fact she has increased the number of calls compared to her usual pattern, Eva self-reports and other objective monitoring variables does not show any situation to far from Eva's usual state…. The NYMPHA system also presents some prediction analysis, based on Evas own data collected over the period of time she has been using the NYMPHA system, of the course of illness for the next days to her, and these does not shown signs of (hypo-)mania.

In the hospital, Maria the nurse taking care of patients through the NYMPHA web interface hasn't noticed any considerable changes in Eva's state besides the variation on number of calls detected by the NYMPHA system, and also the prediction models does not suggest that Eva is currently on her way to gradually enter a (hypo-)manic episode, so she decides to keep monitoring Eva for a couple of days to see if there are any new relevant behavior variations detected by the NYMPHA system.

Hans is the moderator of the NYMPHA online support-group where Eva is usually the most active participant. Hans has noticed that during the past days Eva hasn't been posting her usual supportive messages to other patients as she usually does. This makes him feel worried about Evas condition since she is normally very participative and proactive in the online support-group….For this reason, since he does not have access to any of the NYMPHA data collected from Eva's smartphone and sleep bracelet, he decides calling her to see if everything is fine and discovers that Eva is experiencing a low level of symptoms, so he decides informing Maria about this situation with the accept from Eva. After the call with Hans, Maria decided contacting Eva to have a better assessment on her state.

3 Technical Requirements

The proposed solutions should use smartphones and/or other mobile devices for acquiring self-monitored data and automatically generated behavioural information on a daily basis able to be related to the patients' affective state and able to perform prediction analyses on upcoming changes in state.

The expected solutions should satisfy the minimum number requirements listed below:

3.1 The Mobile Platform

Utilization of a mobile platform guaranteeing adequate operation conditions during the project trials as follows:

Mobile Platform		
Requirements	Description	Minimum Requirements
Battery availability	Efficient usage of monitoring sensors (e.g. setting of adequate data sampling rates, cascade activations of sensors, etc.) in order to guarantee sufficient battery capacity to enable continuous monitoring with limited need to charge the smartphone/wearables.	One day without re-charge for monitoring devices
Multi-parametric objective	The mobile platform should be equipped with sufficient types of sensors for allowing multi-parametric	Availability of sensing instruments to recall objective parameters correlated to mood from at least the following features:

sensing	sensing related to human behavior and mood pertinent to clinical protocols and scales used in bipolar disorder treatment (such as BRAMS, HAMD, etc.).	physical activity location
Memory availability for capturing daily data	The mobile platform requires to have sufficient storage capacity in the client side to collect data from sensors before transferring to the server	At least 1 day of sampling data needs to be stored locally in the sensing devices before uploading to the server
Connectivity from client to server	The mobile platform needs to guarantee access to the server side to transfer multi-parametric data for longer-term storage and analysis. The applicants to the PCP need to detail the connectivity requirements of their proposed solution and guarantee the provisioning of data traffic plans to achieve such data traffic availability.	Provide analysis of the estimated value of minimum required connectivity data traffic for provisioning of the proposed solution
Mobile Platform Usage into Clinical Process	The integration roadmap of the sensing platform needs to be defined at both, 1) at the level of the clinical processes affected by the innovative mobile solutions and 2) at the level of data exchange with the existing clinical systems	1) Plan describing how the mobile platform will operate within the clinical process. 2) Compliance of the solution with HL7

3.2 The Patients' Monitoring System

The proposed solutions shall include a Patients Monitoring System (PMS) able to provide patients and clinicians (and eventually informal caregivers) with the affective state of patients and other potential relevant information to improve the treatment management and the outcomes.

The PMS should define the strategy(ies) in which patient state will be assessed in a clear way (e.g. as a comparison between baseline vs. monitored parameter values, as a comparison of long-term patients' state vs. clinical assessment, etc.). The PMS should be able to analyze and synthesize the subjective and objective data and perform some level of prediction analyses. This meaning that the system should be able to perform ongoing prediction analysis (based on both an individual and group data) and thereby providing forecasts on the course of illness to the clinicians. The patients could receive a notification if data analysis suggests that they could be on their way into a depressive or (hypo)manic state.

The Patients' Monitoring System		
Requirements	Description	Minimum Requirements
Daily collection of self-monitored subjective data	Enable the acquisition of Information collected from patients through self-assessment input about their symptoms of bipolar disorder.	Regarding subjective monitoring, the proposed system should be able to collect at least the following input from patients: - Mood state in a scale considering at least 3 levels (neutral mood, positive mood and negative mood) - Sleep hours self-assessment

		- Medicine intake from self-assessment - Activity level from self-assessment
High level representation of behaviors from sensing data	Enable the representation of high level behaviors related to mood variability such as general lifestyle changes relevant to clinical protocols/scales (e.g. the Young Mania Rating Scale, the Hamilton Depression Rating Scale).	The system should be able to represent at least the following behaviors: - Amount of physical and social activity - Time spent in different locations - Irregularities with sleep
Algorithms for Identification of changes in behavior affecting mood	Development of algorithms for data analysis in order to identify behavior changes impacting on mood variations over time.	The system needs to implement at least one algorithm for detection of behavior variations correlated with mood on daily basis
Representation of objective/subjective data as aggregated value describing mood state	Production of algorithms for enabling aggregated representation of multi-parametric data associated to a single mood value	The system needs to implement at least one algorithm for aggregation of daily data into a single value representing a minimum of 3 different mood levels (negative mood, neutral, positive mood)
Behavior trends analysis for mood forecasts	The subjective and objective data should be analyzed in order to present behavior trends analysis and forecasts of the course of illness for the patients based on collected data from the patient. The system should include predictive models of mood. This in order to support the professionals to make a clinical decision on whether there is an indication to react on the data in the NYMPHA system. The system should not, as standard, present predictions to the patients, but mainly to the professionals.	The system needs to be able to implement at least one report of mood assessment for the previous 5 days and the prediction of minimum 1 day ahead of the mood state.

3.3 The User Interfaces

The personal monitoring system should define the way in which the collected information (subjective and/or objective) will be presented to the different stakeholders involved in the treatment management process. In this way, the relevant User Interfaces (UIs) for clinicians, patients and informal caregivers should be defined considering specific usability issues (e.g. which information will be presented to each stakeholder and how (e.g. aggregated information, detailed sensor information, etc.). The definition of the UIs should take into consideration previous research done on this domain in order to maximize usability and system adoption.

The User Interfaces		
Requirement	Description	Minimum Requirements
Implementation of interfaces for clinicians	Clinical professionals need to be enabled to visualize daily patients' information and care indicators to support the decision making process regarding the treatment. As	Development of: -Patient management system (functionalities of adding, modifying and deleting patients information) -Interfaces for visualizing patients'

	mentioned above should the system be able to analyze and give some prediction/ forecast on potential upcoming depressive or manic episodes. This based on the collected subjective and objective data. The presentation of data to the clinicians is very important and should be as easy and user friendly to get an overview of as possible. It should be possible to go through many patient data at a time without needing to enter too many subpages on the web interface.	historic and predicted mood state as screenshots including group of patients and as single individuals.
Implementation of interfaces for patients	Patients need to be empowered for increasing awareness on their health state through dedicated interfaces in their mobile devices and web interfaces. For these kinds of interfaces, the clinicians need to be able to configure the UIs in accordance with patients in order to include specific items to be monitored to gain awareness of behaviors evolution in specific periods. It should be possible to set up new variables that the patients or clinicians may want to monitor or enter on a daily basis.	Development of: - Interfaces for presentation of detailed information on patient's objective and subjective data for at least 1 week for increasing self-awareness. - Interfaces providing configurable questionnaires for periodic self-assessment of mood.
Implementation of interfaces for informal caregivers	Informal caregivers should be able to interact through simple user interfaces in order to support the patients' treatment and recovery process	Development of: A moderated external interaction mean for patients-informal caregiver exchanges (e.g. wiki, etc.).
Highly intuitive and effective User Interfaces	All user interfaces developed for NYMPHA-MD including clinicians, patients and informal caregivers user interfaces need to be designed in a way to maximize usability and effectiveness leading to high user acceptance of the proposed system. The proposed interactive systems need to perform a User Acceptance Test before the pilot experimentation. Interfaces should consider accessibility standards System usability needs to be verified before the pilot experimentation. System acceptability needs to be carried out after the pilot experimentation.	Provide a UAT plan using a standard methodology (e.g. IEEE 829) for the user interfaces. Provide interfaces able to achieve the following navigation and performance requirements when utilizing the system: - Patient Registration on Clinician Interfaces should be possible in less than 5 minutes for experienced users - Access and Authentication to patients and clinicians interfaces should take less than 2 minutes for experienced users - Visualization of group of patients status interface should take no more than 3 navigation levels (clicks) from the clinicians homepage - Visualization of self-assessment historic data in patients interfaces should take no more than 3 navigation levels (clicks) from homepage - Input of daily questionnaires in patients' interfaces should take less than 5 minutes for experienced users.

3.4 The Data Management

In NYMPHA-MD, Issues concerning data protection will be given serious attention. The proposed solutions need to guarantee compliance with data protection, patient safety, security and privacy regulations in the target countries.

In particular, at the EU level, the data protection regulatory framework is essentially represented by two Directives: Directive95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data and Directive2000/58/EC concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications).

The Data Management		
Requirements	Description	Minimum Requirements
Data Protection	Health related sensitive data should be managed and preserved according to the legal framework on privacy and security issues related to data protection indicated in the EU directives and national laws of the countries participating to the project.	-Directive 95/46/EC and the latest proposal for regulation update released in 2012 need to be applied. - For data storage to be conducted out of hospital environments (e.g. in cloud services) solutions need to be compliant with local regulations on data protection.
Patient Safety	Patient safety needs to be guaranteed looking the safeguard of patients at different levels by protecting data integrity and the quality of the mHealth apps and services	Its required compliance with EC directives 93/42/EEC and the latest 2007/47/EC
Security	Data security should be guaranteed accordingly to the regulations applied in the target cities.	The solutions need to implement access control and a description of how will manage responsibility of data custodian and policies on data sensitivity.
Privacy	Compliance with privacy regulations in the target countries (mandatory rules for privacy according to local regulations need to be implemented such as information consent, voluntary withdrawal at any time, etc.)	- The solutions need to be compliant with Privacy regulations in the target countries - Privacy by design approach needs to be implemented for automatic monitoring
Interoperability	The proposed solutions shall maintain clear observation of the relevant standards for data management and interoperability in health in the target regions and should describe how they intend to comply with main standards in health informatics	The solutions need to explicitly document: - A clear description of how international or European standards (e.g. HL7) will be adopted in the solution

3.5 Clinical Requirements

The clinical requirements in NYMPHA-MD involve aspects related to different aspects of the implementation of mobile health solutions into clinical practice. In particular the requirements define the needs of 1) adaptation of the solutions to the clinical process, 2) the procedures for

patients recruitment, 3) the role and needs regarding the community-based care support, 4) the impact of NYMPHA-MD solutions in the actual costs savings of healthcare provisioning and 5) the required ethical considerations for implementing NYMPHA-MD trials. The details on these points are presented below:

Requirements	Description	Minimum Requirements
Adaptation to clinical process	The proposed monitoring solutions should be adaptable to different clinical workflows and situations in each target country.	The solution needs to explicitly document: A description of how the proposed solution will consider adaptation to operate within different workflows
Patients Recruitment	In the third phase three pilot studies are going to be conducted. In these three pilot studies a number of patients with bipolar disorder experiencing some level of depressive or manic symptoms at each site should be recruited for pilot testing of the proposed monitoring system selected to proceed to the third phase. In these pilot tests collaboration with the local clinicians will be necessary. The local clinicians will conduct the clinical research part of the pilot studies in close collaboration with the applicants involved during this final stage.	The applicants need to provide a description of their strategy for recruiting in collaboration with local clinicians a minimum of 20 patients to be involved in each target site.
Community based-care support	4.3 Community-based Care Support NYMPHA-MD solutions should allow patients interfaces for linking external systems (e.g. blogs, repositories, wikis, etc). for increasing engagement and sharing of static and dynamic resources (i.e. case stories, relevant readings, FAQ, videos, psycho-education materials), on multiple themes related to the disease.	The solution needs to incorporate community-based care support by enabling the patient user interface to access at least one configurable link to an external system (e.g. blog, repository, wiki, etc). The configuration of such functionality needs to be enabled in concordance with clinicians.
Reduction of Cost of Care	4.4 Cost of Care Reductions NYMPHA-MD solutions are envisioned to create a clear benefit not only from clinical and social dimensions but also from economical viewpoint. In particular, NYMPHA-MD should reduce healthcare costs compared to current practice of bipolar disorder treatment. For accessing the third phase of NYMPHA-MD PCP, the proponents should present their plan to achieve the target costs reductions and such reductions need to be described in	The solutions need to explicitly provide a plan aiming to enable a 10% reduction of: •Patients re-admissions to mental health service due to relapse •Patients admissions to inpatient structures •Number of remote consultations/telephone calls with clinical professionals •Number of outpatient visits to clinical professionals

	terms of monetized values.	•Number of home visits from clinical professionals •Time spent on capturing self-assessment information by patients vs. time spent using paper-based self-assessment
Ethical Approvals	Ethical Committee Approval for Usability and Pilot Tests The responsible clinical researcher from each site (Trento, Copenhagen and Catalonia) will need to apply for local ethical approval of the pilot studies to be conducted in the second and third phases of the PCP for the respective usability and pilot tests. The study protocol defining all aspect of the pilot study, including objectives; inclusion and exclusion criteria; sample size etc., will be provided by the researcher at each site. The ethical approval submission will be done by the researchers defining and providing the study protocol including objectives etc. at each site in a timely manner to avoid unnecessary delay of the pilot study process. Different ethical requirements may apply for each country and a close collaboration with the local clinical researcher will be necessary. Liability and indemnities on this regard will be ruled by Ethical Approval requirements applying in each target region while liability for injure to final users due to improper functioning of the proposed solutions is responsibility of the applicants who are responsible for indemnities and insurance previsions.	Applicants need to provide a roadmap on how will be conducted the application to Ethical Approval for the following phases: • Usability tests • Pilot tests in the target sites.